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RESEARCH ARTICLE

PREPARATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF EPERISONE HYDROCHLORIDE BY COMPRITOL ATO 888 AS A MATRIX FORMING AGENT**Dhameliya Pankit B***, Vyas Jigar R, Narola Mahesh, Patel Kinjal, Upadhyay Umesh

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*Corresponding Author's Email: pankitpatel123@gmail.com**ABSTRACT**

Objective: The objective of this work was to prepare and evaluate oral sustained release matrix tablet of highly water soluble drug and to study the effect of proportion of wax and addition of release liner on *in-vitro* release of drug.

Method: The matrix tablets were prepared by melt granulation method using drug:wax in 1:1, 1:2 & 1:3 proportions and evaluated for on *in-vitro* drug release. Then the proportion 1:1 was selected and wax matrix tablets were prepared by three techniques melt granulation, wet granulation and direct compression to check their *in-vitro* release profiles.

Results: The study revealed that Compritol ATO 888 is potent sustained release polymer and released only 72.45% in 24 h even at 1:1 proportion. So, lactose was added as release liner in further study which helped in achieving complete release in 24h.

Conclusion: The present study has concluded that Compritol ATO 888 can be used as matrix-forming agent to control the release of a highly water soluble drug such as Eperisone HCl. It was also observed that melt granulation technique was found more effective. Release liner like lactose may help enhancing the release profile when it is marginally slow.

Keywords: - Eperisone Hydrochloride, Compritol ATO 888, Sustained release, Melt granulation, Release liner

INTRODUCTION

A sustained-release dosage form is defined as “any drug or dosage form modification that prolongs the therapeutic activity of the drug”¹. Development of oral sustained release (SR) tablets of highly water soluble drugs or bioactives has always been a challenge and therefore, opportunity for formulation scientist. Most of these drugs if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic levels and hence will lead to toxic side effects. Sustained delivery of such drugs ensures improved drug delivery and patient compliance, greater safety and efficacy, desired release kinetics and helps in maintaining the plasma drug concentration within the therapeutic window for extended period of time^{2,3}.

Lipids (such as Compritol ATO 888) are considered as an alternative to polymer in the design of sustained drug delivery systems due to their advantages such as the low melt viscosity (thus avoiding the need of organic solvents for solubilization), absence of toxic impurities such as residual monomer catalysis and initiators, potential biocompatibility and biodegradability⁴. However, research data obtained by experiments suggest that Compritol ATO 888 may be recommended as a matrix agent in the development of sustained release formulation in spite of its traditional role as a lubricant.

Lipids like glycerides are a family of excipients which have generated considerable interest in the preparation of oral dosage forms. Some glycerides such as Compritol

ATO 888 (glyceryl behenate), Precirol ATO 5 (glyceryl palmitostearate) can be used for the preparation of sustained release dosage forms⁵. The esterification of glycerol by long chain fatty acid gives them a pronounced hydrophobic character with a low HLB value of 2⁶. Several techniques including melt granulation⁷, melt pelletization⁸, hot melt extrusion⁹ and hot melt coating¹⁰ have been used to obtain sustained release dosage forms from glycerides-based formulations.

Melt granulation (MG) is a solvent-free process which involves the use of a substance that melts at a relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point. The substance acts as a liquid binding agent, and the technique does not require the use of organic solvents. Moreover, in melt granulation drying is not necessary and thus, the process is less consuming in terms of time and energy compared to other methods⁴. Sustained release matrix tablets have been produced with Compritol ATO 888 by various methods including MG¹¹, wet granulation (WG) and direct compression (DC)¹².

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Eperisone Hydrochloride, an established Muscle relaxant acts by relaxing both skeletal muscles and vascular smooth muscles and demonstrates reduction of myotonia, improvement of circulation, and suppression of pain reflex in case of Spastic paralysis, Neck-shoulder-arm syndrome, scapulohumeral periarthritis and low back pain. The melting point of Compritol ATO 888 and Eperisone hydrochloride is 65-77 and 167°C, respectively. Therefore, it is a thermally stable drug and MG technique should not affect the thermal stability of the drug. It has a plasma elimination half-life of 1.6-1.87 h with a usual dosage regimen of 50 mg trice daily. Therefore, to reduce frequency of administration and improve patient compliance, a sustained release dosage formulation of Eperisone Hydrochloride is desirable. The drug is associated with certain side effects such as Shock and anaphylactoid reactions like redness, itching, urticaria and Toxic epidermal necrolysis. Therefore, a properly designed sustained release dosage form of the drug should also minimize fluctuation in blood concentration, reduced risk of side effects and show uniform pharmacological response¹³⁻¹⁵.

Sustained release matrix tablets of Eperisone Hydrochloride have previously been produced using hydrophilic polymers like HPMC, HPC¹⁶. The objective of the present study was to prepare oral sustained release matrix tablet of a highly water soluble drug by MG using Compritol ATO 888, and to evaluate the effect of the concentration of the lipid and presence of release liner on the release of the drug. Such a sustained release formulation, if achieved, would be substantially more affordable than those previously developed.

METHODS

Materials

Eperisone Hydrochloride was a gift from Sharon Bio-Medicine, Mumbai, India while Compritol ATO 888 was obtained free of charge from Gattefosse SAS India. Di-Calcium phosphate, magnesium stearate, lactose, Aerosil 200, isopropyl alcohol, concentrated hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate were purchased from SD Fine chemicals, Mumbai, India. Double distilled water (D.W.) was prepared freshly whenever required. Other chemicals and reagents used were of analytical grade.

Methods

Preparation of Eperisone hydrochloride matrix tablets

Preparation of wax matrix tablets was done by three methods: MG, WG and DC as follows.

Melt granulation method: The wax (Compritol 888 ATO) was melted in a porcelain dish over a water bath maintained at 75-80°C for 3 min and Eperisone Hydrochloride was gradually added with continuous stirring until uniformly mixed. The molten mixture was allowed to cool and solidify at room temperature crushed in a mortar and passed through a 40# sieve. The granules were compressed into flat-faced tablet using multi-station rotary tablet compression machine (Karnavati engineering Pvt. Ltd. India) at a constant compression force.

Wet granulation method: Drug & excipients (except magnesium stearate) were blended geometrically in a mortar and pestle for 15 minutes then wet granulation was performed by addition of IPA in sufficient quantity. dough mass was passed through 16# sieve (ASTM) and dried at 35-40°C for 15 min. dried granules were passed from 40# sieve and compressed into tablets using multi-station rotary tablet compression machine.

Direct Compression method: All the ingredients were passed from 60# sieve (ASTM) and directly compressed into tablet using multi-station rotary tablet compression machine.

Evaluation of drug - Excipient interaction: The pure drug, wax and the matrix tablet formulation were subjected to IR spectroscopy using FT-IR spectrophotometer (Shimadzu – 8400, Japan). Their spectra were obtained over the wave number range of 4000 – 400 cm⁻¹.

In-vitro drug release: *In vitro* release studies were conducted using USP type II paddle apparatus (VDA-6D USP Std -VEEGO) run at 50 rpm. The buffer was kept at thermostatically controlled temperature of 37±0.5°C. The test was carried out in 900 ml of 0.1 M HCl for 2 h and then replaced with phosphate buffer (pH 6.8) as the dissolution medium for another 22 h. The pH change of medium was effected by adding 4.32 g of sodium hydroxide and 6.08 g of potassium dihydrogen phosphate dissolved in 5 ml water to the previous acidic medium (0.1 M HCl)¹⁷. Five milliliters samples were withdrawn at the time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h and replaced with equal volume of fresh dissolution medium. The samples were filtered through 0.45 µm filter and analyzed for drug content at 260 nm by UV spectrophotometer.

The release profile of prepared tablets was matched with the set values of drug release at different time points, mentioned below

Initial 2 h	20-30%
At 8 th h	50-60%
At 14 th h	70-80%
At 20 th h	NLT 85%

Drug release kinetics: To determine the mechanism of drug release from the formulations, the data were subjected to zero-order (Eq 1), first order (Eq 2) and Higuchi (Eq 3) release kinetics^{18, 19}

$$M_t = M_0 + k_0 t \dots\dots\dots (1)$$

$$\ln M_t = \ln M_0 + k_1 t \dots\dots\dots (2)$$

$$M_t = M_0 + k_H t^{1/2} \dots\dots\dots (3)$$

where M_t is the cumulative amount of drug released at any time, t , and M_0 is the dose of the drug incorporated in the delivery system. k_0 , k_1 and k_H are rate constants for zero-order, first order and Higuchi models, respectively. The dissolution data were also fitted according to the well-known exponential equation of Peppas²⁰, as in Eq 4, which is often used to describe drug release behavior from polymeric systems.

$$M_t/M_\infty = kt^n \dots\dots\dots (4)$$

Where, M_t/M_∞ is the fraction of drug released at time t , k is the kinetic constant, and n is the diffusional exponent for drug release. The diffusion exponent, n , is dependent on the geometry of the device as well as the physical mechanism of release. Zero order release describes a release rate independent of drug concentration while the Higuchi square root kinetic model describes a time dependent release process. The value of n indicates the drug release mechanism; if $0.1 < n < 0.5$, Fickian diffusion is indicated while $0.5 < n < 1$ indicates non-Fickian diffusion.

Mean dissolution time: MDT is the mean time for the drug to dissolve under in vitro dissolution conditions.

$$MDT_{in-vitro} = \frac{\sum_{i=1}^n t_{mid} \Delta M}{\sum_{i=1}^n \Delta M} \quad \dots\dots\dots (5)$$

Where,

i = the sample number, n is the number of dissolution samples,

t_{mid} = the time at the midpoint between i and $i - 1$,

M = the additional amount of drug dissolved between i and $i - 1$

MDT value is used to characterize the drug release rate from the dosage form and the retarding effect of the polymer. As it is readily apparent, the higher the polymer level, the higher the value of MDT and the greater the retarding effect of the polymer (21).

Area under curve: AUC is the area under the curve (mathematically known as integral) in a plot of concentration of drug in blood plasma against time. The AUC (from zero to infinity) represents the total drug exposure over time. Assuming linear pharmacodynamics

with elimination rate constant K , one can show that AUC is proportional to the total amount of drug absorbed by the body (i.e. the total amount of drug that reaches the blood circulation). The proportionality constant is $1/K$.

In present study, AUC is calculated for in vitro drug release by plotting graph of %CDR versus time using Eq. (6)

$$(AUC)_0^t = \int_0^t \left(\frac{C_n + C_{n+1}}{2} \right) X (t_n - t_{n-1}) \quad \dots\dots\dots (6)$$

Where,

C = % cumulative drug release,

t = time point,

AUC was used for the optimization purpose here. % difference in AUC values can give idea about comparative drug release amount in 24h. It was applied when other statistical parameters were giving similar results. Here, profiles showing 10% difference in AUC were considered as dissimilar.

RESULTS AND DISCUSSION

Interaction between drug and wax was checked by FT-IR Spectroscopy. As shown in Figure 1, the major IR peaks observed in the spectra for tablet formulation were, the sharp absorption band of the conjugation carbonyl group around 1674 cm^{-1} ($C=O$) and 1604 cm^{-1} ($C=C$), $-N-H$ stretch at 1566 cm^{-1} , $C-H$ bend at 1465 cm^{-1} , which are characteristic of Eperisone Hydrochloride. When this is compared to the spectra of the formulations, it would appear that there was no obvious interaction between drug and the Compritol ATO 888.

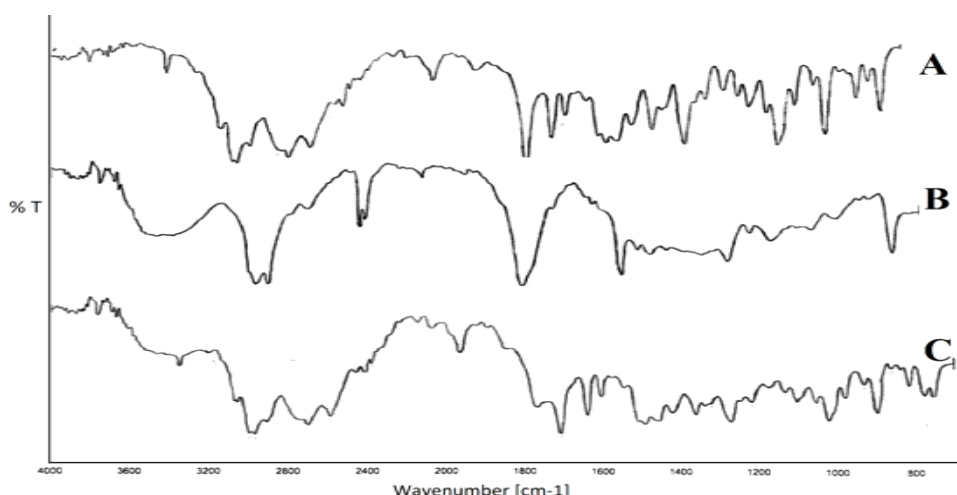


Figure 1: FTIR spectra of Eperisone hydrochloride (A), Compritol ATO 888 (B) and tablet formulation containing all the Ingredient (C).

Wax matrix tablet of Eperisone Hydrochloride was prepared by MG in three different proportion (1:1, 1:2, & 1:3) and effect of proportion of wax matrix on *in-vitro* release profile of drug was studied.

Table 1: Composition of Eperisone Hydrochloride matrix tablets

Ingredients	F1 ^a	F2 ^a	F3 ^a	F4 ^a	F5 ^b	F6 ^c
Eperisone Hydrochloride	150	150	150	150	150	150
Compritol 888 ATO	150	300	450	150	150	150
Lactose				30	30	30
Polyvinyl pyrrolidone K30				15	15	15
Di-Calcium Phosphate				12	12	12
Magnesium Stearate				3	3	3
Total	300	450	600	360	360	360

* All amount in mg/tablet

To keep the formulation uniform, ingredients required to be added in WG & DC have also been added in MG in F4.

a -Tablets prepared using melt granulation.

b -Tablets prepared using wet granulation.

c -Tablets prepared using direct compression

In-vitro release study revealed that the drug was 72.45 ± 2.9 , 56.43 ± 2.3 , and $41.66 \pm 2.0\%$ cumulative drug release at the end of 24 h for formulations F1, F2, and F3, respectively. Thus, indicating that drug release fell as the wax content of the tablets increased. The difference in release rate between the batches was statistically significant (Similarity factor f_2 values were 46.86 and 32.55 respectively for F2 and F3 with that of F1).

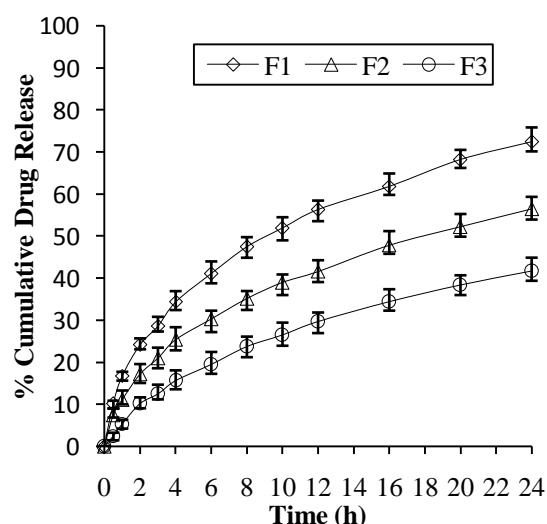


Figure 2: Effect of different concentration of Compritol ATO 888 on *in-vitro* release of formulation of eperisone hydrochloride matrix tablets.

As the study aimed to develop 24 h release profile, none of the above fits completely. But, with change in composition or change in the method, the goal may be achieved in 1:1 composition. Further batches were prepared by different techniques like WG, & DC. Addition of lactose was done as release liner along with other ingredient, keeping drug:wax proportion constant at 1:1.

Optimized proportion was further compared with other methods like Wet granulation and direct compression along with addition of lactose as release liner. Comparison of the three methods of formulation used

indicate that sustaining effect from the tablets prepared by Wet granulation (F5, 99.12% in 20h) and direct compression (F6, 99.25% in 16h) were significantly higher ($p < 0.05$) than from the equivalent formulation made by melt granulation (F4, 98.62% in 24h)

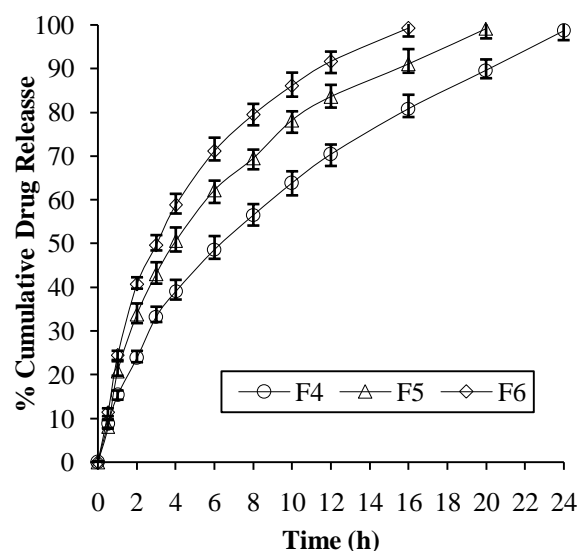


Figure 3: Comparative *in-vitro* Release profiles of sustained release matrix tablet made by MG (F4), WG (F5) and DC (F6), in the ratio of 1:1.

Drug release kinetics: Table 2 shows that the best-fit release kinetic data with the highest values of regression coefficient (r^2) were shown by Higuchi models and zero order. The values of n were in the range of 0.502 to 0.693 (i.e., between 0.50 – 0.89) exhibits non-fickian (anomalous) transport in which the drug was delivered by combined effect of diffusion and polymer relaxation (21). Data of r^2 indicate that Peppas models also suitably described the release of Eperisone hydrochloride from the matrix tablets. None of the formulation exhibited first order kinetics.

Table 2: *In vitro* release kinetics of Eperisone hydrochloride matrix tablets

Formulation Code		F1	F2	F3	F4	F5	F6
Zero order		0.876	0.898	0.932	0.925	0.865	0.856
Fist order		0.719	0.737	0.684	0.722	0.621	0.655
Higuchi		0.991	0.996	0.994	0.997	0.983	0.980
Peppas Model	r ²	0.99	0.994	0.979	0.991	0.945	0.956
	N	0.502	0.521	0.693	0.611	0.624	0.593
	K	16.26	11.46	5.28	15.35	18.37	22.80
AUC		1237.31	935.24	654.27	1347.47	1602.97	1559.65
MDT		15.11	22.34	35.9	8.19	5.83	4.42

Influence of proportion of Wax on in-vitro drug Release.

As shown in figure 2 as ratio of polymers increased from 1:1 to 1:3, it resulted into greater retardation of drug release. This might be due to an increased polymer concentration resulting in a decrease in the total porosity of the matrices (initial porosity plus porosity due to dissolution of the drug), decreasing the penetration of the dissolution medium into the matrix system and thus reducing drug dissolution. In addition, increasing the polymer content led to an increase in the drug diffusion path length, which in turn retarded drug diffusion from the matrix²¹. As stated earlier, based on kinetic analysis of release data, Eperisone hydrochloride release occurred by a non-Fickian diffusion mechanism. The initial drug release (i.e., in the 2 hour) of 23.80, 33.74, and 40.62% for F4, F5 and F6, respectively, may be attributed to 'burst' release of the drug on the tablet surface irrespective to method of formulation.

Influence of method of formulation on Release

Influence of method of formulation on Release was also studied. Results obtained from DC and WG method indicated negligible role of binding agent in release retardation, thus suggesting use of MG as the most effective method in sustaining Eperisone hydrochloride release. Figure 3 shows release profile of Compritol ATO 888 in 1:1 ratios prepared by MG (F4), WG (F5) and DC (F6). These results are in accordance with previously published results.^{12, 21} In case of MG, lesser drug release is occurring because of complete and proper coating of melted wax on drug particles which forms uniform hydrophobic wax matrix through the tablet. So, here penetration of dissolution medium to the matrix will be low hence dissolution occurs at slower rate. However, in case of matrices prepared by DC or WG, it seems that the dissolution of drug particle at surface of matrices allowed the establishment of channels through which drug was released.

Relative retardation can be ranked depending upon method of formulation as –

Melt granulation > *Wet granulation* > *Direct compression*

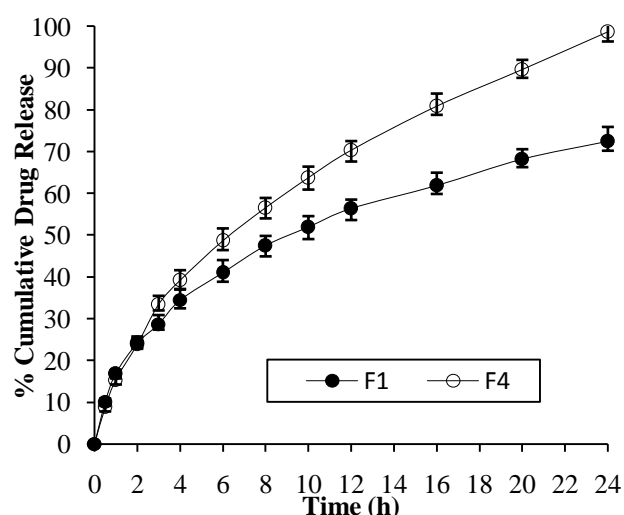


Figure 4: Comparative *in-vitro* release profile of F1 and F4 to study influence of Lactose on release

Influence of release liner on in-vitro drug Release.

As shown in figure 4 addition of 10% lactose as release liner can give significant (26.17%) rise in release. F4 gives high initial release as well as higher release of drug over the time range of experiment. However, release of both batches matches to zero order and higuchi kinetic data. Still MDT decreases from 15.11h to 8.19h at the same wax concentration as lactose was added.

Thus, the *effect of additives* like lactose, MCC, DCP on release of drug from matrices has been well established and it is also known to control and differ the initial release & release over time period. In present research and Studies done before shows that by including water soluble diluents such as lactose, near zero order release also can be achieved from matrix system^{12, 21}. The overall mechanism of release of the drug from glyceryl behenate matrices appeared to be a diffusion-controlled mechanism. The data of drug release were fitted to the *Higuchi's square root of time model*. The mechanism of this evidence indicated that the prepared tablets behaved as inert matrices. Visual observation of the tablets during the dissolution studies revealed that the tablets remained intact without any significant change in their shape. These observations support our conclusion that the release of the drug is mainly due to diffusion through the

channels formed in the matrix. These channels are formed due to rapid dissolution of the drug particles on the surface of the matrix and the presence of the water-soluble release enhancers like lactose. Then, the dissolution medium would penetrate these channels allowing for more dissolution of the drug present in the deeper sites of the matrix.

It was observed that the values of AUC were higher when lactose was added in formulation F4 to F6. WG method was showing highest value of 1602.97 but, it could not retard the release upto 24 h. However, MG process was found to be best fitting to all other criteria with satisfactory AUC value of 1347.47 which was found best among all other formulations.

CONCLUSION

The study showed that Compritol ATO 888 is an appropriate waxy matrix former for sustained release of highly water-soluble drug such as eperisone hydrochloride. Drug release was diffusion-controlled

(non-fickian) and achieves almost near to zero order in all the formulations.

MG technique fits completely into the predetermined parameter and criteria whereas, other two techniques lack behind. Extended release profiles can be achieved by any of three methods using Compritol ATO 888 at higher proportion but MG technique achieved 24 h release profile with lesser amount of was as compare to other methods.

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CONFLICT OF INTEEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES

- Gudsoorkar VR, Rambhau D. Influence variable of process one standard drug release from disintegrating sustained release Ibuprofen beads. *The Eastern Pharmacist* 1997, 40(2), 111-113.
- Siddique S, Bose A, Khanam, J. Modulation of drug (metoprolol succinate) release by inclusion of hydrophobic polymer in hydrophilic matrix. *Drug Dev Ind Pharm* 2011, 37(9), 1016-1025.
- Deore RK, Kavitha K, Tamizhmani TG. Preparation and evaluation of sustained release matrix tablets of tramadol hydrochloride using glyceryl palmitostearate. *Trop J Pharm Res* 2010, 9(3), 275-281.
- Heng WS, Wong TW. Investigation of melt agglomeration process with hydrophobic binder in combination with sucrose stearate. *Eur J Pharm Sci* 2003, 19(5), 381-393.
- Bodmeier RA, Swarbrick J, Boylan JC. Eds. Encyclopedia of pharmaceutical technology. 2nd ed. Vol. III, New York, Marcel Dekker Inc; 1998.
- Hamdani J, Moes AJ, Amighi K. Physical & thermal characterization of Precirol & Compritol as lipophilic glycerides used for the preparation of controlled release matrix pellets. *Int J Pharm* 2003, 260, 47-57.
- Zang YE, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. *Drug Dev Ind Pharm* 2003, 29, 131-138.
- Hamdani J, Moes AJ, Amighi K. Development and evaluation of prolonged release pellets obtained by melt pelletization process. *Int J Pharm* 2002, 245, 167-177.
- Lloanusi NO, Schwartz JB. The effect of wax on compaction of microcrystalline cellulose beads made by extrusion and spheronization. *Drug Dev Ind Pharm* 1998, 24, 37-44.
- Jannin V, Cuppok Y. Hot-melt coating with lipid excipient. *Int J Pharm* 2013, 457, 480-487.
- Mahaparele PR, Kasture PV, Deshmukh SS et al. Sustained release matrices of Metoprolol succinate using Compritol 888 ATO and Precirol ATO 05. *J Pharm Res* 2006, 5, 10-14.
- Patere SN, Desai NS, Jain AK et al. Compritol® 888 ATO a lipid excipient for sustained release of highly water soluble active, formulation, scale-up and IVIVC study. *Current Drug Del* 2013, 10, 548-556.
- The Japanese Pharmacopoeia, Japanese society of Pharmacopoeia, 15th ed. 2012.
- Sweetman SC, Martindale: The Complete Drug Reference. 36th ed. London, UK: Pharmaceutical Press, 2009.
- Mi JK, Hyeong SL, Yook HN, et al. Pharmacokinetic interaction between eperisone hydrochloride and aceclofenac: A randomized, open label, crossover study of healthy Korean men. *Clin Thera* 2013, 35, 1528-1535.
- Viveksarathi K, Rajarajan R, Kannan K, Manavalan R. Dosage form design and evaluation of eperisone hydrochloride matrix film coated extended release tablets, *Int J Pharm Pharm Sci* 2012, 4(2), 575-581.
- Patel NM, Soniwala MM. Influence of release enhancer on release of Venlafaxine HCL from Glyceryl Behenate matrix tablet. *Indian Drugs* 2008, 45, 98-104.
- Harland R, Dubernet C, Benoit JP, Peppas N. A model of dissolution-controlled, release from non-swellable polymeric microspheres. *J Control Rel* 2003, 6, 282-291.
- Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. *J Pharm Sci* 1963, 52, 1145-1149.
- Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm* 1983, 15, 25-35.
- Shady M, Amin A, Gawad N. Comparative study on the different techniques for the preparation of sustained-release hydrophobic matrices of a highly water-soluble drug" *Drug Disc Thera* 2010, 4(6), 484-492.